The Impact of Standards on Determining the Approvability of Multiplexed RNA-based In Vitro Diagnostic Tests

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Device Classification

Class I devices - general control requirements

Class II devices - special controls and general control requirements.

Class III devices - high risk with no established predicates, or raises new types of questions of safety and effectiveness

Device Classification (cont.)

General controls:

- registration and listing
- Good Manufacturing Practices (GMPs)
- premarket notification (510(k)), unless exempt
- prohibition of adulterated, misbranded, or banned devices
- record keeping
- reporting of device failures

Device Classification (cont.)

Special controls:

-performance standards

-postmarket surveillance

-patient registries

-guidelines/guidances

-design control

-tracking requirements

Pathways to the Market

- IVD may be exempt
- Premarket notification - 510(k)
- Premarket approval - PMA
- Product development protocol - PDP
- Humanitarian device exemption - HDE
- Analyte specific reagent - ASR

Major Elements of a Submission

- Intended use/indications for use
- Performance characteristics
  - Analytical
  - Clinical
- Labeling (package insert)

Intended Use/Indications for Use

- Determine the type of review
- Determine the data requirements
- Describes what the device measures and why and the target population(s)

Performance Characteristics - Analytical

- Characterization of components
  - Array
  - Controls
  - Calibrators (Quantitative)
  - Signal detection systems
  - Instruments e.g. robotic arrayers, scanners, imagers, thermal cyclers etc.
  - Instrument software

Performance Characteristics - Analytical

- Characterization of components
  - Array
    - Design and fabrication e.g. platform type, surface type, composition and spatial layout, number of elements (spot), number of replicates, etc.
    - Spot elements e.g. clone, sequence, PCR primer pairs, probe length, gene name, etc.
    - Built-in controls e.g. housekeeping genes, etc.

Performance Characteristics - Analytical

- Characterization of components
  - Controls
  - Calibrators (Quantitative)
  - Signal detection systems
  - Instruments e.g. robotic arrayers, scanners, imagers, thermal cyclers etc.
  - Instrument software

Performance Characteristics - Analytical

- Samples
  - Type and source
  - Storage and handling conditions
  - Extraction, purification, amplification (if needed) and labeling
  - Sample quality assessment

Performance Characteristics - Analytical

- Reproducibility – within chip, between chips, day-to day, between sites, inter-operators, lot-to-lot?
- Accuracy
- Assay sensitivity
- Assay specificity and interfering substances
- Data processing and statistical analysis
- Stability of reagents and chip

Performance Characteristics - Clinical

- Clinical sensitivity – the ability of the test to correctly identify the presence of disease.
- Clinical specificity – the ability of the test to correctly identify the absence of disease.

Current Use of Standards

- Reference methods
- Reference materials/standards
  - Limited
  - Source – WHO, NIST, CDC, NIH etc.
  - Calibrators and controls
    - Traceability
    - Assign values
    - Standardize and control assay performance

Examples of Standards

- Reference materials
  - WHO PSA standard
  - WHO RF standard
  - NIST standards for therapeutic drugs
  - Various infectious disease reference materials (CDC, WHO and others)
  - NIH cytokine standards

Microarray Controls

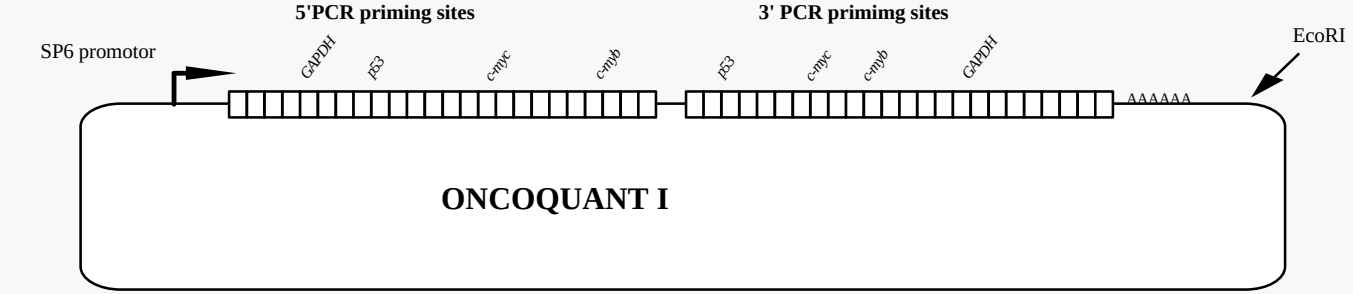
- Internal controls
  - Housekeeping genes
  - Synthetic RNA e.g. Oncoquant (CBER)
- Pooled RNA from cell lines
- Pooled RNA from test samples
- RNA and oligonucleotides from plants and bacteria

Synthetic RNA

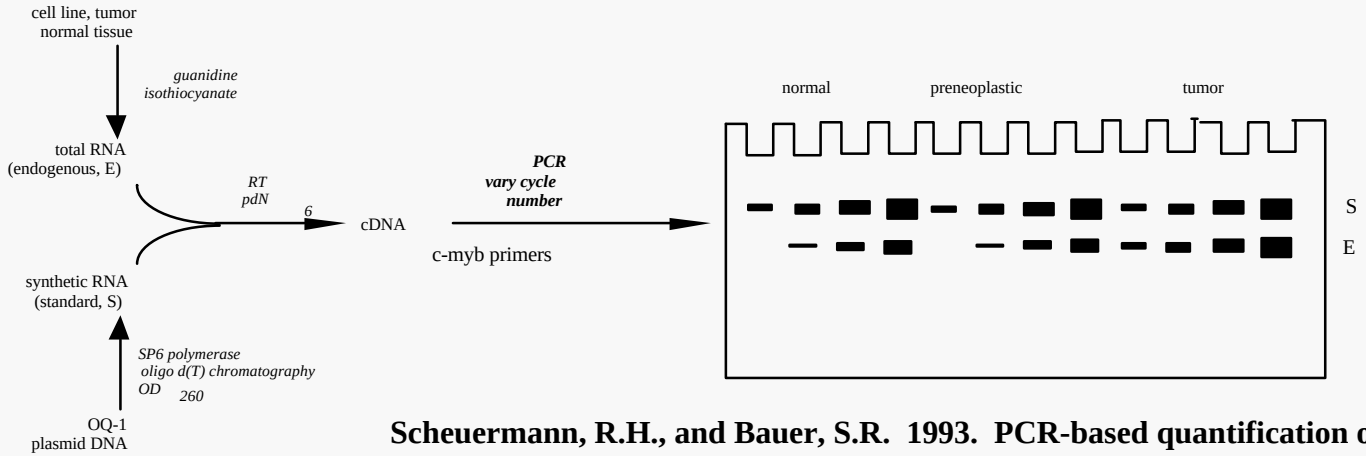
- Internal standard
- Unique sequences (can be customized)
- Controls for reverse transcription, labeling, hybridization, instrumentation
- Quantify RNA abundance
- Assess RNA quality of sample
- Stable

Oncoquant

A. STANDARD RNA PRODUCTION



B. RNA QUANTIFICATION



Scheuermann, R.H., and Bauer, S.R. 1993. PCR-based quantification of multiple mRNA species: a method for the analysis of oncogene expression. Methods in Enzymology 218: 446-473.

Universal RNA Reference

- Pooled human cell lines
  - Normal, tumor or combination?
  - How many cell types?
  - How many cell lines?
  - Availability? Source?
  - Quality of cell lines?
  - Batch-to-batch variability

Next Step